PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Efficacy of the Gelstix nucleus augmentation device for the treatment of chronic discogenic low back pain: protocol for a randomised, sham-controlled, double-blind, multicentre trial
AUTHORS	Koetsier, Eva; van Kuijk, Sander; Maino, P.; Dukanac, J.; Scascighini, L.; Cianfoni, A.; Scarone, P.; Kuhlen, D.E.; Hollman, M; Kallewaard, Jan-Willem

VERSION 1 – REVIEW

REVIEWER	Cornish, Rosie University of Bristol, School of Social and Community Medicine
REVIEW RETURNED	12-Jul-2021

GENERAL COMMENTS	This is a very clearly written protocol. I have no specific comments.

REVIEWER	Manchikanti, Laxmaiah Pain Management Center of Paducah
REVIEW RETURNED	10-Aug-2021

GENERAL COMMENTS	Authors in this manuscript described a “Protocol for a Randomized Sham-Controlled Double-blind Multicenter Efficacy Study of the Gelstix™ Nucleus Augmentation Device to treat Chronic Discogenic Low Back Pain.” Overall, the study is well designed. If the methodology as described and modified, it will be appropriate and clinically relevant. Specific comments are as follows: Background and Rationale: Authors describe multiple manuscripts related to discogenic low back pain; however, they missed one manuscript (Manchikanti L, et al. Evaluation of the relative contributions of various structures in chronic low back pain. Pain Physician 2001; 4:308-316), which actually shows a different perspective, other than internal disc disruption with a prevalence of 26%. Further, 40% may not be an accurate numbers. It may be more appropriate to quote as 26% to 40%. Second paragraph starting with 26-11, starting with medical history, physical examination, may use additional references including 16-19. Authors may use reference 1 in other areas with minimally invasive treatments, etc.

	Concept of Gelstix is encouraging. The sham intervention appears to be appropriate; however, sodium chloride solution in itself may have active effects. Authors may consider injection of sodium chloride solution outside the disc to avoid any type of activity and keep it pure placebo control. Even then, a no treatment group would be the most appropriate control to add to if it is feasible. Outcome measures are appropriate; however, in sample size calculation, 30 patients per group will be required to have 80% power to detect a minimally, clinically relevant difference of 1.5 on the NRS between groups. This difference may not be clinically relevant. Authors should consider a higher parameter such as at least 3-point reduction and/or 50% improvement from baseline pain. Adding these factors may increase the number of patients required, specifically with no treatment group, and may become difficult to incorporate. At least authors should discuss these issues.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Dr. Rosie Cornish, University of Bristol

Comments to the Author:

This is a very clearly written protocol. I have no specific comments.

Reviewer: 1
Competing interests of Reviewer: None declared.

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Reviewer: 2

Dr. Laxmaiah Manchikanti, Pain Management Center of Paducah

Comments to the Author:

Authors in this manuscript described a “Protocol for a Randomized Sham-Controlled Double-blind Multicenter Efficacy Study of the Gelstix™ Nucleus Augmentation Device to treat Chronic Discogenic Low Back Pain.”

Overall, the study is well designed. If the methodology as described and modified, it will be appropriate and clinically relevant.

ANSWER: Thank you Dr. Laxmaiah Manchikanti. It is an immense honor that you reviewed our manuscript as I greatly admire your work.

Specific comments are as follows:

Background and Rationale: Authors describe multiple manuscripts related to discogenic low back pain; however, they missed one manuscript (Manchikanti L, et al. Evaluation of the relative contributions of various structures in chronic low back pain. Pain Physician 2001; 4:308-316), which actually shows a different perspective, other than internal disc disruption with a prevalence of 26%. Further, 40% may not be an accurate numbers. It may be more appropriate to quote as 26% to 40%.
ANSWER: Thank you for this reference and advice. We modified 40% to 26-40% and we have added the reference. (see reference 9).

Second paragraph starting with 26-11, starting with medical history, physical examination, may use additional references including 16-19.
ANSWER: Thank you for this comment. We have added the following references:
- Laslett M, Oberg B, Aprill CN, et al. Centralization as a predictor of provocation discography results in chronic low back pain, and the influence of disability and distress on diagnostic power. Spine J 2005;5:370-80.
- Laslett M, Aprill CN, McDonald B, et al. Clinical predictors of lumbar provocation discography: a study of clinical predictors of lumbar provocation discography. Eur Spine J 2006;15:1473-84.
- Manchikanti L, Soin A, Benyamin RM, et al. An update of the systematic appraisal of the accuracy and utility of discography in chronic spinal pain. Pain Physician 2018;21:91-110.
- McCormick ZL, DeFrancesch F, Loomba V, et al. Diagnostic Value, Prognostic Value, and Safety of Provocation Discography. Pain Med 2018;19:3-8.

Authors may use reference 1 in other areas with minimally invasive treatments, etc.
ANSWER: Thank you. We added reference 1 to the sentence: 'If conservative treatment fails, (minimally) invasive treatments are considered.' In the introduction part of the manuscript.

Concept of Gelstix is encouraging.

The sham intervention appears to be appropriate; however, sodium chloride solution in itself may have active effects. Authors may consider injection of sodium chloride solution outside the disc to avoid any type of activity and keep it pure placebo control. Even then, a no treatment group would be the most appropriate control to add to if it is feasible.
ANSWER: We agree, and we thank you for these considerations. However, meanwhile we already started the study and included many patients, and therefore we cannot change these methods anymore. We have now added the following text to the limitation section (only the underlined text is added):
Another limitation of this trial is the question whether intradiscal saline injection is a true placebo, as it may have active effects. For example, a recently published systematic review and meta-analysis of Manchikanti et al. showed that epidurally administered saline and saline with steroids may be both effective in managing low back and lower extremity pain.66 On the other hand, saline has been routinely used as a sham intervention in several other intradiscal treatment studies such as the randomized controlled trial (RCT) of Kallewaard et al.,30 which compared intradiscal methylene blue plus lidocaine to intradiscal saline plus lidocaine injection, and two the RCT's of Cao et al.49 and Khot et al.50 comparing intradiscal corticosteroid to saline injection in the treatment of discogenic low back pain. To reduce the risk of a bias due to the uncertainty saline injection being a true placebo, a third 'no treatment group' (receiving only physiotherapy treatment) could be added to this study. However, we regard adding a third 'no treatment group' to this study not feasible, mainly because of the expected difficulties in patient recruitment.

Outcome measures are appropriate; however, in sample size calculation, 30 patients per group will be required to have 80% power to detect a minimally, clinically relevant difference of 1.5 on the NRS between groups. This difference may not be clinically relevant. Authors should consider a higher parameter such as at least 3-point reduction and/or 50% improvement from baseline pain. Adding

these factors may increase the number of patients required, specifically with no treatment group, and may become difficult to incorporate. At least authors should discuss these issues.
ANSWER: The current sample size calculation makes sure that we have sufficient power to detect differences between groups of as small as 1.5 points. Hence, bigger differences will be easier to detect if present in the data (for example, defining the MCID to be 3 points, keeping all other assumptions equal, would require only about 9 participants per group). Some studies suggest the MCID to be about 2 points in chronic pain patients, but this is based on studies looking at within-patient change from baseline, not differences between groups [Farrar et al, 2001, doi: 10.1016/S0304-3959(01)00349-9]. We are of the opinion that differences between groups of less than 2 points can still be of clinical relevance. All results of our study will be interpreted not just from the perspective of statistical significance, but predominantly from the perspective of clinical meaningfulness.
We have chosen not to base our primary outcomes on a dichotomization of change in pain intensity as this reduces information into a crude success/ no success variable.

Reviewer: 2
Competing interests of Reviewer: None

All authors have contributed significantly to this work and all authors are in agreement with the content of the manuscript and agree to submission to BMC Open.